REMARKS

Claims 1 – 19 are pending in the application. Claims 1, 12, 15 and 16 have been amended. Basis for the amendments to claims 1 and 12 can be found at paragraphs [00013] – [0015] of the published application; and the bases for the amendments to claims 15 and 16 can be found in Example 1 of the published application. New claim 18 has been added. Basis for new claim 18 can be found in Example 1, page 4, of the application as filed and at paragraph [0019] of the published application. New claim 19 has been added. Basis for new claim 19 can be found at paragraph [0011] of the published application. Therefore, the amendments and new claims do not add any new matter within the meaning of 35 U.S.C. §132. Claims 10-11 have been cancelled without prejudice or disclaimer to the subject matter contained therein.

Accordingly, entry of the amendments is respectfully requested.

1. Rejection of Claims 15-17 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 15-17 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the application regards as the invention. The Examiner asserts that the rejected claims refer to "Example 1", and it is unclear which "Example 1" is meant based on the fact the specification contains an "Example 1" and a "Comparative Example 1." Applicants respectfully point out that claim 17 has been incorrectly included in the rejection. Applicants do not see how claim 17 directly or indirectly recites the limitation "Example 1" and kindly ask the Examiner for clarification of the basis for inclusion of claim 17 in this rejection. Applicants respectfully confirm that the Examiner correctly assumes that the referenced Example falls on page 4 of the application as filed and paragraph [0019] of the published application

The Examiner recommends that including a page number of the referenced Example in the rejected claims would be sufficient to overcome this rejection. Applicants greatly thank the Examiner for his suggestion. Applicants, however, respectfully submit that claims 15-16 have been amended to include the necessary language of Example 1.

Accordingly, the claims are definite and distinct and the Examiner is respectfully requested to withdraw this rejection.

2. Rejection of Claims 1-17 under 35 U.S.C. §103(a)

The Examiner has rejected claim 1-17 under 35 U.S.C. §103(a) as being unpatentable over Ruchatz et al in EP 09 55063 ("Ruchatz") in view of Erni et al CH 663788 ("Erni").

The Examiner suggests that one of skill in the art attempting to prepare new anti-inflammatory compositions comprising Carprofen would start with Ruchatz, which is used as the primary reference in this rejection. Ruchatz discloses a large list of potentially active agents which does not include Carprofen. Applicants respectfully submit that Erni is the proper primary reference, because Ernie is directed to the use of salts of Carprofen in the preparation of an anti-inflammatory composition. Thus, one of skill in the art when looking to provide a new injectable Carprofen preparation would not look to Ruchatz. Instead, the skilled artisan would look to Erni.

Erni discloses salts of Carprofen for use in the preparation of anti-inflammatory compositions (see claim 6). Particularly, Erni discloses new salts of Carprofen, namely 6-chloro-alpha-methylcarbazol-2-acid, with a basic alpha-amino acid, either L-Lysine or L-Arginine, with the former being more preferable. Erni teaches the advantages of the salts as being increased bioavailablity over the free salt (see page 2, column 2, lines 21 to 25). Erni also teaches that the salts may be used in a liquid foam, e.g. as solutions, suspensions or emulsions.

Erni does not disclose a room temperature stable injectable solution for veterinary use or a solution comprising from 0.25 to 30% (w/v) of Carprofen or a physiologically acceptable salt of Carprofen, and from 0.5% to 20% (w/v) of a poloxamer and water q.s.

Additionally, known Carprofen formulations typically require controlled chilled storage at 2 to 8°C, and such refrigeration, cool room or chiller cabinet storage gives rise to poor syringability of the currently available products.

Thus the instant problem to be solved by the present subject matter in light of the art is to provide a new Carprofen formulation having enhanced stability at room temperature. The solution to this problem lies in the use of poloxamers in combination with the Carprofen.

The advantageous results of the present subject matter are illustrated on page 9, lines 10 to 17 where a formulation of the present subject matter has been studied over a period of 11 months at ambient temperatures without loss of potency being observed. In particular, the trial formulation was assayed as containing 5.16% Carprofen on manufacture, 5.10% after 7 months and 5.26% after 11 months; these apparent differences being accounted for by slight moisture loss.

Furthermore, the room temperature stability of the product of the present subject matter has the added advantage of improved syringability when compared to the currently available formulations (see, for example page 2, lines 20 and 21 of the specification). The formulations of the present invention also have the advantage that they produce low side effects, for example reduced or lack of local irritation (see page 9, lines 5 to 9 of the specification).

Although Example 4 of Erni discloses that a polyoxamer may be used as a suppository base for the administration of the Carprofen and Lysine salt. Erni neither describes nor teaches in any way, the usefulness of poloxamers in solution and how they might increase the room temperature stability of pharmaceutical preparations containing

Carprofen or salts thereof. Applicants therefore respectfully submit that Erni does not render claim 1 of the instant application obvious.

It is further submitted that claim 1 is nonobvious over Erni even if Erni is combined with Ruchatz for the reasons outlined below.

Ruchatz describes the use of an aqueous composition for subcutaneously or intramuscularly administering drug formulations. The composition comprises a combination of a polyoxyethylene-polyoxypropylene (Copolymer (A)) with a weight average molecular weight of 8,000 to 20,000; and a polyoxyethylene-polyoxypropylene (Copolymer (B)) with a weight average molecular weight of 4,000 to 8,000 and an active pharmaceutical ingredient. Ruchazt does not disclose Carprofen. Therefore one of skill in the art would not consider Ruchazt as relevant to the problem of providing a Carprofen formulation which has enhanced stability at room temperature. Even if the skilled artisan did consider the teachings of Ruchatz, there is nothing in this reference to teach that the use of poloxamers would lead to enhanced room temperature stability of the active agents. It would therefore not be obvious to one of skill in the art modify the references to arrive at the present subject matter in the light of Erni and Ruchatz. In view of the foregoing Applicants respectfully submit that the instant set of claims is nonobvious over the cited art.

Notwithstanding the above, if the Examiner maintains his view that Ruchatz is the closest art, Applicants respectfully maintain that the present subject matter is patentable over the cited documents for the reasons outlined below.

The Examiner has suggested that Ruchatz discloses an injectable composition that contains: anti-inflammatory agents (for example ibuprofen); polyethylene polyoxypropylene copolymer system (a poloxamer); and organic solvents.

The Examiner alleges that the only difference between Ruchatz and the present subject matter is that Ruchatz does not disclose Carprofen. He states that Emi discloses Carprofen salts useful for the preparation of analgesic pharmaceutical anti-inflammatory and antirheumatic compositions, and it would therefore be obvious to use Carprofen in the composition of Ruchatz to arrive at the instant subject matter. Applicants respectfully submit, however, that the Examiner is mistaken in this regard for the reasons outlined below.

Ruchatz does <u>not</u> disclose a composition which is a room temperature stable injectable solution and which is suitable for intravenous injection, as required by the instant claims. The Ruchatz compositions are sol-gel compositions. There is no disclosure that the Ruchatz compositions are room temperature stable, as required by the present claims. Nor are they suitable for intravenous injection, as further discussed below.

Sol-Gel

The Ruchatz compositions sol-gel can be administered at room temperature in liquid form intramuscularly and subcutaneously, and at body temperature they form a slow release gel, from which the active ingredients are released in a controlled way. (See paragraph [0018]) It would therefore be clear to the skilled artisan that the Ruchatz compositions, if administered intravenously, would possibly be lethal. This is supported

by paragraph [0035] of Ruchatz which states that the Ruchatz compounds gel at body temperature.

Hence, Ruchatz is not directly relevant to the present subject matter because it relates to compositions that form depots upon injection subcutaneously or intramuscularly. Such compositions are not suitable for intravenous administration.

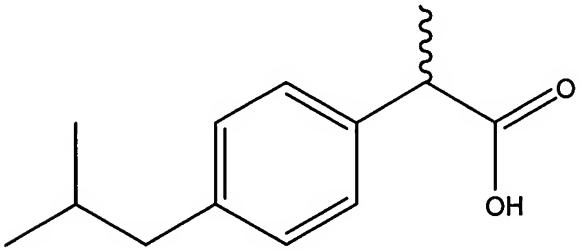
Small animals, especially cats, are notoriously difficult to administer drugs intravenously due to the relatively small diameter of veins, and sparsity of suitable veins to inject into. Hence, any sol-gel depot formation would be disastrous if the teaching of Ruchatz was to be followed.

Interchangeability

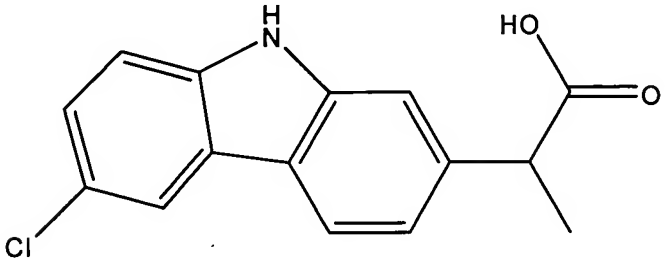
The Examiner has also stated it would be obvious for one of skill in the art to interchange ibuprofen of Ruchatz with Carprofen to arrive at the present subject matter. However, Applicants respectfully submit that the interchangeability of the instant subject matter and Ruchatz is not as the Examiner suggests. Notwithstanding the above arguments that Ruchatz is directed to sol-gel compositions, whereas the instant subject matter is directed to a solution suitable for intravenous injection which is room temperature stable, the skilled person would not simply replace the Ibuprofen of Ruchatz with Carprofen. Paragraph [0022] of Ruchatz warns that active ingredients used in the compositions can influence the viscosity characteristics of the compounds. For example, ibuprofen leads to a lowering of the gelling temperature. If, as the Examiner states, the skilled artisan would expect Ibuprofen and Carprofen to act in similar ways then, Ruchatz would lead the skilled artisan away from using poloxamers with Carprofen. The skilled artisan would be lead away from the instant subject matter, because the lowering of the

gelling temperature would be the exact opposite of the requirements of the present subject matter, since gelling would make this product unsuitable for intravenous administration, and the lower the gelling temperature the worse it gets for intravenous use. Thus, Ruchatz does not lead to the instant subject matter.

The chemical structures of ibuprofen and Carprofen are given below:



Ibuprofen 2-[4-(2-methylpropyl)phenyl]propanoic acid



Carprofen 2-(6-chloro-9*H*-carbazol-2-yl)propanoic acid

Notwithstanding the above, ibuprofen and Carprofen are very different chemical entities, and hence the skilled artisan would not expect their interchangeability without proper experimental evidence, especially in light of the teachings of Ruchatz (see paragraph [0022]).

In any case, as outlined above, Ruchatz would not lead the skilled artisan to the present subject matter, since Ruchatz is directed to an ibuprofen containing sol-gel composition for subcutaneous or intramuscular administration. In contrast, the present subject matter is directed to an aqueous intravenous injectable composition comprising Carprofen.

Methods for the Production of Ruchatz, et al.

Ruchatz describes two methods for the production of the Ruchatz subject matter:

1) "The Cold Process" (see paragraph [0016]). This method requires that poloxamers to be dissolved in water at 0 to 25 °C. Insoluble components can be dissolved in an organic solvent like ethanol, i-propanol and propylene glycol, and can then be homogeneously combined with the aqueous phase.

2) "The Hot Process" (see paragraph [0017]). In this method, the co-polymers are dissolved as in The Cold Process but using a temperature of 60 to 100°C, and the solution is then cooled to 25 °C. In both of these processes active agents that are not-water soluble are dissolved in an organic solvent prior to mixing with water to form the injectable composition.

In contrast, Applicants have surprisingly found that although for example ibuprofen and Carprofen have similar insolubilities in water, i.e. of less than 1mg/ml, they have found that unlike the process of Ruchatz, which first require ibuprofen to be dissolved in an organic solvent, then the addition of water, in the present subject matter Applicants have found that Carprofen, poloxamer and water may simply be added together at room temperature, and mixed until they form a clear solution. This is unexpected and new as Carprofen is not recognized as being water soluble.

Unexpected/Surprising Properties of the Present Composition

Applicants submit that the advantages of the present subject matter are clearly described in the paragraph abridging pages 2 and 3 of the present application. As discussed in the specification, known injectable Carprofen products on sale are called Rimadyl injectable (and as disclosed in EP280887A) are suitable for intravenous

administration. See Figure 1 for the pharmacokinetic comparison. The Rimadyl injectable composition requires the presence of cholanic acid and a lipid, and the product needs to be stored at 4°C to ensure stability for months or more. Applicants respectfully submit that no such pharmacokinetic comparison could be carried out between the Ruchatz subject matter and the instant subject matter, since the Ruchatz composition is for the slow release of an active from a depot formed by the mixture of poloxamers gelling at body temperature when injected intramuscularly or subcutaneously. This would give a very different bioavailability profile to an intravenously administered composition (it is likely that such a composition would have a longer Tmax and lower Cmax. Instead of Figure 1 showing overlapping data, the Ruchatz peak would be expected to occur later, be lower and would last for much longer than our product peak).

Applicants respectfully submit that the instant formulation is a totally new formulation which is substantially different to the Rimadyl injectable product (see Fig. 1) (lipid based formulation). Applicants have maintained bioequivalence with this product (see, for example, paragraphs 1, 3 and 4 of page 9 and Table 1). It would not be obvious to arrive at the present subject matter in the light of the cited art. Advantageously, the composition of the present matter has a simpler composition. It is room temperature stable, and consequently it is room temperature storable unlike Rimadyl injectable / EP280887A.

In view of the foregoing, Applicants submit that it would not be obvious for the skilled artisan to arrive at the instant subject matter.

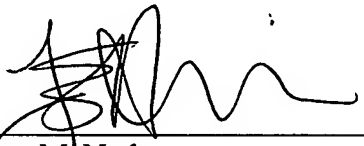
CONCLUSION

In light of the foregoing, Applicants submit that the application is in condition for allowance. Applicants respectfully request that the Examiner contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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present subject matter.